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What a second booster dose of mRNA COVID-19 vaccines tells us

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Real-world studies have shown waning vaccine effectiveness against both SARS-CoV-2 infection and COVID-19-related hospitalisation within 2·5 months after a first booster dose of COVID-19 mRNA vaccine, especially for the SARS-CoV-2 omicron (B.1.1.529) variant.[1] Several countries have thus recommended a second booster dose of COVID-19 mRNA vaccine (ie, a fourth vaccine dose) in older and immunocompromised individuals at higher risk for severe disease, hospitalisation, and death.

In Israel, protection conferred by a fourth dose of BNT162b2 (Pfizer-BioNTech) was shown against both SARS-CoV-2 infection[2] and COVID-19-related hospitalisation and death[3] in those aged 60 years or older. These clinical data are supported by immunological data from an open-label, non-randomised study conducted in Israel in health-care workers receiving a second booster dose of COVID-19 mRNA vaccine at least 4 months after the first booster dose. Individuals who received the second booster had ten-fold higher neutralising antibody titres against wild-type SARS-CoV-2 and the delta (B.1.617.2) and omicron variants compared with participants who had only received the single booster.[4]

In *The Lancet Infectious Diseases*, Alasdair P S Munro and colleagues[5] report a randomised sub-study of 166 participants nested within the original phase 2 COV-BOOST trial. This sub-study investigated the safety, reactogenicity, and immunogenicity of a second booster dose of mRNA COVID-19 vaccines (full-dose BNT162b2 or half-dose mRNA-1273 [Moderna]) administered around 7 months following a first booster dose of BNT162b2. Participants had been primed with either two doses of BNT162b2 or two doses of ChAdOx1 nCoV-19 (Oxford-AstraZeneca). The safety profile was favourable. Pain was the most common local solicited adverse event and fatigue was the most common systemic solicited adverse event, and no serious adverse events were related to the second booster dose.

In the primary immunogenicity analysis population, comprising only participants who were nucleocapsid-seronegative before receiving the second booster and had no history of symptomatic COVID-19, the fold changes in anti-spike protein IgG titres from before (day 0) to after (day 14) the fourth dose were 12·19 (95% CI 10·37–14·32) and 15·90 (12·92–19·58) in the BNT162b2 and mRNA-1273 groups, respectively. Furthermore, there was around a 5–8-fold increase in cellular response against wild-type, beta (B.1.351), and delta SARS-CoV-2 after the second booster.

Three interesting results were highlighted. First, the anti-spike protein IgG titres 14 days after the second booster dose for both mRNA vaccines were 1·5–2·2-fold higher than the peak titres after the first booster dose of BNT162b2. This finding contradicts the hypothesis that the maximal immunogenicity of mRNA vaccines is achieved after three doses and a fourth dose merely restores antibody concentrations. Second, humoral responses increased to similar levels in the older (≥70 years) versus younger (<70 years) age groups, with fold changes in anti-spike IgG titres between the first and second booster being higher in the older age group than in the younger age group. This result is important because the second booster dose was first recommended in Israel, the USA, and Europe for older people, despite no data on immunogenicity and safety being available for older age groups. Finally, there seems to be a maximum anti-spike protein IgG titre and T-cell response (a possible ceiling effect). Indeed, in some seronegative participants with high humoral and cellular responses before the fourth dose, the increase in immunogenicity following the second booster was limited; this result was replicated in those with a history of SARS-CoV-2 infection before the second booster dose. Considering the high level of omicron variant circulation in countries where the second booster is recommended, this point could prompt reconsideration or delay of the second booster.

In summary, this randomised trial shows that fourth booster doses of mRNA COVID-19 vaccines (full-dose BNT162b2 and half-dose mRNA-1273) given 8 months after the previous dose can boost humoral and cellular responses at least to the level following the first booster, with a good safety profile, in all age groups. Unfortunately, data on neutralising antibodies against variants were not reported.

We believe that the future of COVID-19 vaccine booster campaigns should be rethought in the light

of rapid waning of post-booster immunogenicity and immune escape of new variants of concern. Heterologous boosters with next-generation vaccines, such as multivalent vaccines (vaccines providing protection against different variants simultaneously), universal coronavirus vaccines, vaccines eliciting stronger T-cell responses, or mucosal vaccines (either intranasal or oral), are among the future options for COVID-19 vaccination. However, while awaiting these next-generation vaccines, booster immunisations are crucial to restore vaccine effectiveness against severe outcomes in clinically vulnerable populations. The results of this trial are important to help policy makers to determine who benefits most from booster dosing and when booster dosing should be implemented. The question of whether benefit can be gained with longer delays between boosters remains unanswered.

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